



RAPID COMMUNICATION

ABH and Lewis antigen distributions in blood, saliva and gastric mucosa and *H pylori* infection in gastric ulcer patients

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are a good indicator for cellular alterations in the gastric epithelium.

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Abstract

AIM: To investigate the ABH and Lewis antigen expression in erythrocytes, saliva and gastric epithelium, as well as the association between *H pylori* and the presence of gastric epithelial lesions.

METHODS: The distribution of ABH and Lewis blood group antigens in erythrocytes, saliva and gastric mucosa of *H pylori*-infected gastric ulcer patients was analyzed. Forty-two patients with gastric ulcer were studied, and fifty healthy individuals were used as control group. The blood group antigens were determined by direct hemagglutination, dot-ELISA and immunohistochemical methods in erythrocytes, saliva and gastric mucosa specimens, respectively. Diagnosis for *H pylori* infection was performed by conventional optical microscopy and ELISA.

RESULTS: A higher seroprevalence of IgG *H pylori* specific antibodies was observed in gastric ulcer patients (90%) compared to the control group (60%). We observed a significant increase of phenotypes O, A₂ and Lewis b in *H pylori*-infected patients. The expression of these antigens had progressive alterations in areas of ulcerous lesions and intestinal metaplasia.

CONCLUSION: ABH and Lewis blood group antigens

INTRODUCTION

The presence of *H pylori* in gastric mucosa is associated with chronic active gastritis and more severe gastric diseases, including chronic atrophic gastritis, peptic ulcers, stomach cancer, and lymphoma^[1, 2]. However, only a minority of *H pylori*-infected patients develop gastric diseases. In order to explain this fact, the influences of additional factors such as the genetic predisposition of the host and the genotype of *H pylori* strains have been analyzed^[3]. Biochemical studies^[4, 5] have discovered a blood group antigen binding adhesin (BabA), which can mediate bacterial adherence to epithelial cells and seems necessary for *H pylori* pathogenicity by facilitating the subsequent action of the other virulent factors such as VacA and CagA. Borén *et al*^[6, 7] demonstrated that the receptors for *H pylori* on gastric epithelial cells are the H and Le^b antigens of the ABH and Lewis (Le) blood group systems. It has been known for decades that individuals of O blood group phenotype have a higher risk of developing duodenal ulcers^[8, 9] and also a higher incidence of gastric ulcers^[8, 10]. In ulcer disease patients infected with *H pylori* little is known about the presence of ABH and Lewis antigens in erythrocytes, saliva and gastric epithelium. However, alterations in these blood group antigen expressions have been extensively described in stomach cancer and precursor lesions^[11, 12]. This study was to investigate the ABH and Lewis antigen expression in erythrocytes, saliva and gastric epithelium

Table 1 Distribution of ABO and Lewis phenotypes in erythrocytes and saliva of gastric ulcer patients and controls

Lewis erythrocytes	Saliva		Secretor	Lewis phenotypes Blood/Saliva	ABO Phenotypes									
	Le ^a	Le ^b			A ₁		A ₂		B		AB		O	
					I	II	I	II	I	II	I	II	I	II
Le (a+ b-)	+	+	S	Concordant	1	2	1	-	-	1	1	-	2	-
Le (a- b+)	+	+	S	Concordant	1	7	2	2	1	7	-	1	12	20
Le (a- b-)	-	-	S	Concordant	-	2	-	-	-	-	-	-	2	-
	+	+	S	Discordant	3	-	1	1	4	-	-	-	7	7
	-	+	S	Discordant	1	-	-	-	1	-	-	-	2	-
Total					6	11	4	3	6	8	1	1	25	27

I = gastric ulcer patients, II = control, S = secretor status

in *H pylori*-infected patients as well as the association of *H pylori* status with these blood group phenotypes and the presence of gastric epithelial lesions.

MATERIALS AND METHODS

Patients and control sample

The study included a total of 42 patients with gastric ulcer who were examined by routine upper endoscopy at Ofir Lioila Hospital (Belém, PA, Brazil) between May and December 2000, and comprised 76% males (32/42) and 24% females (10/42). The mean age was 53 years, ranging 28-80 years. Blood and saliva samples and gastric biopsy specimens were collected from each patient. These selected patients did not take non-steroidal anti-inflammatory drugs, H₂ receptor antagonists, proton pump inhibitors or antimicrobial drugs for at least 60 d before the samples were obtained. Peripheral blood and saliva samples were collected from 50 patients asymptomatic for gastric diseases. These patients did not receive upper endoscopy. The mean age of these individuals was 49 years, ranging 25 - 80 years. This study was approved by the Ethics Committee at the Tropical Medicine Nucleus of the Pará Federal University and informed consent was obtained from the patients before sample collection.

Histopathological analysis of gastric biopsies

For histological analysis, biopsies from the ulcer lesion border and the adjacent area (perilesion) of each patient were obtained. Paraffin-embedded biopsy specimens were sectioned at 4 µm thickness and stained with haematoxylin - eosin and evaluated using the Sydney classification^[13] with regard to the presence of intestinal metaplasia (IM) and the degree of granulocytic and lymphocytic infiltration (mild, moderate, severe). The density of *H pylori* was determined in the sections using a modified Gram staining and graded into absent, mild, moderate and strong, based on the above classification system^[13].

Serological detection of specific antibodies against *H pylori* and *CagA*

The serum samples were tested for IgG-class antibodies against *H pylori* by an indirect hemagglutination assay and anti-*CagA* with a commercial kit based on recombinant *Helicobacter* antigens p120 EIA. Both tests were performed according to the manufacturer's instructions (Viva

Diagnostika, Hürth, Germany). *H pylori* infection diagnosis of the control group was performed using only serological methods. However in the ulcer disease patients *H pylori* status was determined by serological and conventional optical microscopic methods.

Detection of ABO and Lewis blood group antigens

Blood and saliva samples were collected after the endoscopy. In blood the ABO and Lewis phenotypes were determined with a conventional direct hemagglutination technique. The characterization of ABH and Lewis specificities in saliva was tested using the dot-ELISA technique on nitrocellulose^[14]. Immunohistochemistry for ABO and Lewis blood group antigen expression in gastric biopsies (ulcer lesion border and perilesion) in the foveolar and fund epithelium was performed using an indirect immunoperoxidase technique^[15]. The reaction pattern of these antigens in gastric mucosa was classified as positive (homogeneously with more than 50% of stained cells or heterogeneous with 5-50% of stained cells) and negative (without or lower than 5% of stained cells).

Statistical analysis

Statistical tests using Bioestat 3.0 were performed to verify the significance of the differences observed in our study^[16]. The chisquaretest (χ^2) was used as a global test for any relationship. The Mann-Whitney U test was used to compare unpaired data. Spearman's rank and contingency correlation tests were used to examine the relationship between density of *H pylori*, polymorph nuclear activity and chronic inflammation. $P < 0.05$ was considered statistically significant.

RESULTS

Seroprevalence of *H pylori* infection and *CagA* strains

Endoscopic diagnosis of patients with gastric ulcer indicated 74% (31/42) ulceration in the antral region and 26% (11/42) in the corpus region. The presence of IgG *H pylori* specific antibodies was observed in 90% (38/42) of all patients. Approximately 84% (32/38) of these *H pylori*-infected patients were also *CagA* seropositive. In the control group, seroprevalence of IgG *H pylori* specific antibodies was observed in 60% (30/50) of the individuals and 36% (18/50) were also infected with *CagA* strains. These distributions were significantly lower in *H pylori*-infected patients than in gastric ulcer patients ($P < 0.01$).

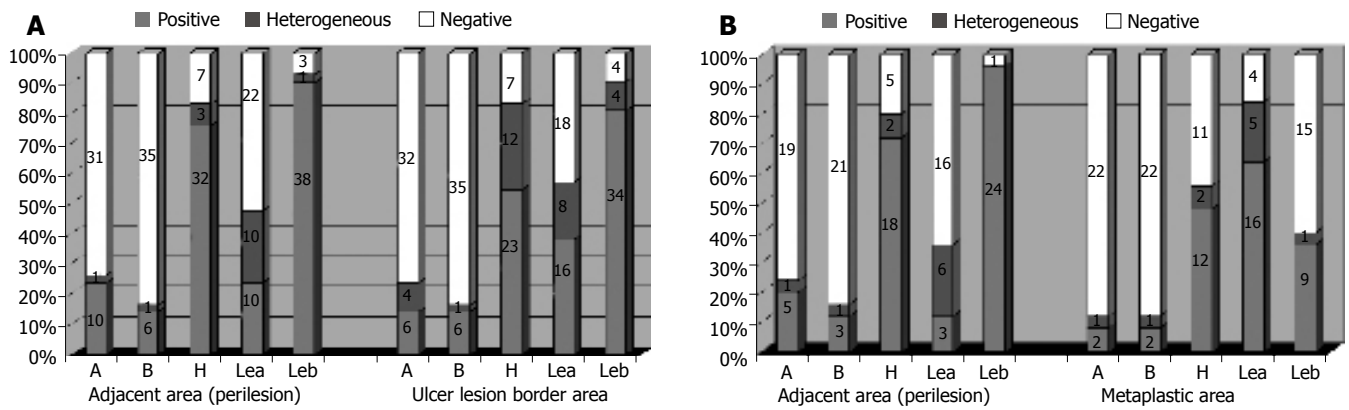


Figure 1 ABO and Lewis antigen distribution pattern in ulcer lesion borders (A) and intestinal metaplastic area (B) of gastric ulcer patients.

Distribution of ABO and Lewis phenotypes in erythrocytes and saliva of patients and control group

A comparison of the ABO blood group phenotype distributions in blood and saliva of gastric ulcer patients and control group is showed in Table 1. Regarding the Lewis blood group system in saliva, the Le^b antigen was detected in approximately 95% of the patients and in the control group. The distribution frequency of ABO ($P>0.05$) and Lewis saliva ($P>0.05$) phenotypes observed in gastric ulcer patients had no difference in relation to the control group. We observed a discrepancy in the expression of Lewis antigens in erythrocytes and saliva in some patients (Table 1), which were divided in two groups: concordant (individuals with similar expression of Lewis antigens in blood and saliva) and discordant (individuals with different expressions of Lewis antigens in blood and saliva). A discordant phenotype was observed in 57% (24/42) of the patients. Of these, 83% (19/24) belonged to the negative erythrocyte Lewis phenotype. A difference in the blood and saliva Lewis antigen expression (Table 1) was observed in only 22% (11/50) of the control group.

Distribution of ABH and Lewis antigen expression in gastric mucosa regions

The pattern of ABH and Lewis antigen distribution in the foveolar epithelium of the perilesion areas compared with ulcer lesion borders showed a loss of A, H and Leb antigen expression, resulting in a decrease of homogeneous expression and an increase in the heterogeneous pattern. At the same time, an increased expression of Le^a antigen was observed in the ulcerous lesion border areas (Figure 1A). The presence of incomplete intestinal metaplasia (IM) was observed in 25 out of 42 ulcer patients. In these patients the same abnormal pattern of ABH and Lewis blood group antigen expression was found to be more intensive, with a significant increase ($P<0.01$) in the expression of Le^a antigen and a decrease in A, H and Le^b antigen expression (Figure 1B).

Correlation of ABH and Lewis blood group antigen expressions in saliva, erythrocytes and foveolar epithelium of gastric mucosa

In the perilesion area of the foveolar gastric epithelium,

Table 2 Distribution of ABO and Lewis blood group phenotypes in relation to serological diagnosis of H pylori infection in ulcer patients and controls

Blood group phenotypes	<i>H pylori</i> infection					
	N	Patients ^a		N	Controls ^b	
		Positive	Negative		Positive	Negative
A ₂ Le(a-b+) ou	27	26	1	30	25	5
O Le(a-b+)						
A ₁ /AB/B/Le(a-b+) ou O Le(a-b-)	15	12	3	20	5	15
Total	42	38	4	50	30	20

^a $P>0.05$ vs bacterial density, lymphocytic and granulocytic infiltration

the ABH antigen expression was in agreement with that in erythrocytes and saliva. All the patients belonging to the A blood group (10/42) expressed antigens A and B. Six of them also expressed antigen H. Likewise, patients of the B blood group (a total of six) expressed antigen B, antigen H was expressed in four of them. Patients of AB blood group expressed antigens A and B. Antigen H was expressed in all O blood group patients (a total of 25 individuals). Analysis of the Lewis phenotype in the perilesion region showed a similar antigen expression pattern to that in saliva of all patients, including those with discordant Lewis phenotypes in saliva and blood. Only one patient had discordant and concordant expression with the erythrocyte phenotype.

Association of ABH and Lewis blood group antigen distribution with H pylori infection and histopathological findings

The Lewis saliva phenotype was used to associate *H pylori* status and the development of gastric ulcers, because this expression was similar to that in the foveolar epithelium in gastric biopsies. Furthermore, the presence of ABO and Lewis antigens in the control group was determined only in saliva and erythrocytes but not in gastric mucosa. In relation to the seroprevalence of *H pylori* infection, a significantly higher level was observed in a defined combination of O-/A₂ Le (a-b+) blood groups than in the set of other blood group phenotypes of the control group (Table 2). However, no significantly different proportions were found in this subdivision, a finding that

might be explained by the high prevalence of the infection. A significant positive correlation was found between bacterial density and degree of chronic inflammation ($P < 0.05$) as well as the polymorph nuclear activity ($P < 0.05$). The degree of chronic inflammation was found to be positively correlated with polymorph nuclear activity ($P < 0.01$). Subsequently, no significant correlation was found by contingency analysis for the variability of histological scores in regard to bacterial density between O-/A₂ Le (a-b+) individuals and the set of other blood group phenotypes ($P > 0.05$), lymphocytic ($P > 0.05$) and granulocytic infiltration degrees ($P > 0.05$) in biopsies from ulcer patients.

DISCUSSION

The sero-prevalence of IgG *H pylori* specific antibodies is 90% in patients with gastric ulcer, much higher than in asymptomatic individuals (60%). Additionally, the *cagA* seropositive phenotype shows a significant association with gastric ulcer patients. The frequencies obtained in patients agree with the reported results in previous studies^[17], in which a high rate of infection was found in symptomatic adults. The same occurs with the rate obtained in asymptomatic adults. This fact also corroborates the studies of seroprevalence in developing countries, which describe a 60% infection rate in the adult populations^[18, 19]. The Lewis blood group antigens in saliva and blood of patients and the control group demonstrated a high frequency of discordant Lewis phenotype. Among these individuals, most of them were grouped in the non-genuine negative Lewis phenotype according to the Ørntoft classification^[20], where Lewis antigens are present in saliva but not in the erythrocytes, which is different from the genuine Lewis phenotype, in which the Lewis antigens are present neither in saliva nor in erythrocytes. The expression of ABH and Lewis blood group antigens in the foveolar epithelium in perilesion areas was similar to that observed in saliva, with no differences in relation to the normal synthesis of these antigens. This can be explained by the fact that circulating Lewis antigens in the serum are only acquired by red cell membranes^[21]. In some physiological conditions and diseases, such as neoplasia, a reduction in the synthesis of these antigens can occur, so that the quantities of these antigens in the blood are not sufficient to be detectable by serological methods, however the salivary phenotypes do not alter^[21]. Probably, the increased degree of inflammation in the gastric mucosa due to infection with *H pylori*, affects the metabolism of glycoconjugates, leading to a decrease in the quantity of Lewis antigens circulating in the plasma. The ABO blood group phenotype frequencies in ulcer patients and the control group were not different. This finding is in contradiction to many studies, which have described the increased prevalence of ulcers among O group individuals^[9, 10].

An interesting finding of our study is the observation that all A₂ subgroup individuals were *H pylori* positive, which has been described in another study regarding gastritis patients^[18]. The reason for this finding is not clear. Theoretically, the qualitative structural difference between

A₁ and A₂ subgroups is based on glycosphingolipids expressed in erythrocytes, so that A₁ transferase is more efficient for converting specific carrier types (H type 3 chains or H type 4 chains) into a determinant than A₂ transferase, resulting in a higher level of H epitope in A₂ subgroup, almost like that in O blood group^[20]. Therefore, we believe that analogue fucosylated structures might exist as a mucosal gastric component relating to the different A subgroups, since glycosphingolipids present in gastric mucosa can function as receptors for the bacterium^[22]. Besides, complex gangliosides (i.e. repetitive N-acetylglucosamine units, fucose branches and di- or multivalency) have been demonstrated in the binding assays as preferred structural requirements for mediating *H pylori* adherence to gastrointestinal epithelial cells^[23].

Furthermore, our study regarding ABO and Lewis phenotype and *H pylori* infection indicated that individuals with O Le (a-b+) and A₂ Le (a-b+) phenotypes had a tendency towards a higher rate of *H pylori* infection. Studies performed by Bóren *et al.*^[6, 7] in 1993 and 1994 have suggested that *H pylori* uses carbohydrate structures with terminal fucose as receptors in the gastric mucosa containing Le^b and H blood group specificities. Later on, Ilver *et al.*^[5] in 1998 and Gerhard *et al.*^[24] in 1999 showed that there is a higher susceptibility to *H pylori* infection in individuals of O and Le^b blood groups, because they have a higher quantity of fucosylated antigens.

In the current study, the association of ABH and Lewis blood group phenotype distributions with the histological scores was not significantly different. But if one considers that Le^b is absent only in 2 out of 42 patients, this result is inappropriate for comparison with other histopathological studies^[25-27]. By comparing the ABH and Lewis antigen expression between the ulcerous lesion border and the adjacent areas (perilesion), we observed an increase in the heterogeneous expression pattern, demonstrating the loss of A, H and Le^b antigen expression and appearance of Le^a reactivity in inflammation regions. Colonization of the gastric mucosa by *H pylori* is a relevant factor that can alter the normal pattern of homogeneous expression.

Some studies have demonstrated that the expression of these blood group antigens is altered in metaplastic areas^[17, 28]. The main alterations described are the increase of Le^a and the decrease of H and Le^b antigens, as was also found in this study. One explanation for this observation is the repression of the secretor enzyme activity, leaving more type I precursor chains available to be transformed into Le^a by the Lewis enzyme, consequently reducing the expression of the H antigen and its transformation into A and/or B and Le^b antigens in these tissues^[29].

In conclusion, the rate of *H pylori* infection seems to be higher among O, A₂ and Le(a-b+) phenotype individuals. The pattern of Lewis expression changes in ulcer disease patients with *H pylori* presence, mainly in intense inflammation and/or intestinal metaplastic areas, showing the increase of Le^a and loss of H and Le^b antigens in the gastric mucosa. Therefore, it is important to understand how ABH and Lewis antigens are regulated in gastric cancer, as well as the interaction of these histo-blood group antigens with *H pylori* adhesion, which needs to be further investigated.

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